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Research Letter to the Editor

Is there an "asymptote of gain" beyond which further increases in cardiorespiratory fitness convey no addition benefits on mortality and atrial fibrillation?

Sae Young Jae, PhD[1,6], Sudhir Kurl, MD[2], Hyun Jeong Kim, MS[1], Barry A Franklin, PhD[3], Setor K Kunutsor, PhD[4], Mira Kang, MD[5], Jari A Laukkanen, MD[2,7]

[1]Department of Sport Science, University of Seoul, Seoul, South Korea. [2]Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland. [3]Preventive Cardiology and Cardiac Rehabilitation, William Beaumont Hospital, Royal Oak, MI, USA. [4]Translational Health Sciences, Bristol Medical School, University of Bristol, Learning & Research Building (Level 1), Southmead Hospital, Bristol, BS10 5NB, UK. [5]Center for Health Promotion, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea. [6]Graduate School of Urban Public Health, University of Seoul, Seoul, Republic of Korea; [7]Faculty of Sport and Health Science, University of Jyväskylä, Jyväskylä, Finland.

Corresponding Author:

Sae Young Jae, PhD.

Health and Integrative Physiology Laboratory, Department of Sport Science, University of Seoul. 90 Jeonnong-dong, Dongdaemun-gu, Seoul 130-743, South Korea.

E-mail : syjae@uos.ac.kr, Phone : 82-2-6490-2953 Fax: 82-2-6490-5204

Abbreviation

ACM = all-cause mortality

AF = atrial fibrillation

CVM = cardiovascular mortality

Fitness = cardiorespiratory fitness

HRs = hazard ratios

METs = metabolic equivalents

PA = physical activity

SCD = sudden cardiac death

To the Editor:

The debate exists on whether the dose-response relation between physical activity (PA) and mortality benefits is in fact curvilinear, U-shaped, or J shaped curve.[1,2] Cardiorespiratory fitness (fitness), highly reflective of habitual PA, is a strong protective of varied adverse health outcomes including cardiovascular disease (CVD)[3,4] and is also associated with lower health care costs.[5] It has been suggested that high fitness levels may be at least as important as lower body mass index in CVD prevention.[6] However, there is still uncertainty whether an upper limit or plateau exists for the cardioprotective effects of increased levels of fitness.[4] In this study, we aimed to evaluate the dose-response relationship between fitness and cardiovascular outcomes and to identify the upper threshold of benefit due to increasing levels of fitness.

Patients and Methods.

The study included 2,368 subjects (aged 42-61 years) from an ongoing population-based prospective cohort study in eastern Finland (the Kuopio Ischemic Heart Disease Study). Fitness was directly measured via peak oxygen uptake (VO_{2peak}, ml/kg/min) during an electrically braked cycle ergometer exercise test to volitional fatigue/exhaustion. VO_{2peak} was defined as the highest attained value for oxygen consumption and/or a plateau in oxygen uptake at maximal exercise, and expressed as metabolic equivalents (METs; 1 MET = 3.5 mL O_2/kg/min). Levels of fitness were categorized according to peak metabolic equivalents (<5 [the lowest], 5-6.9, 7-8.9, 9-10.9, 11-13, and >13 METs [the highest]) attained. The outcomes were defined as all-cause mortality (ACM), cardiovascular mortality (CVM), sudden cardiac death (SCD) and atrial fibrillation (AF) ascertained from hospital notes and discharge lists, death certificates, informant interviews, health practitioner questionnaires, electrocardiograms, medico-legal reports and vital statistics offices from study enrollment until the end of 2014. To

characterize shapes or the dose-response nature of the associations, hazard ratios (HRs) were calculated within the categories of baseline peak METs and plotted against mean peak metabolic equivalent within each category using floating absolute risks.

Results.

During a median follow-up of 25 years (interquartile ranges: 18-27 years), 1,116 ACM, 512 CVM, 221 SCD, and 440 AF occurred, respectively. The figure 1 shows the dose-response nature of the relationships between levels of peak METs and cardiovascular outcomes. After adjusting for age, body mass index, smoking, systolic blood pressure, total cholesterol, glucose, C-reactive protein, and PA level, the risk of ACM decreased gradually with increasing peak METs in a continuous dose-response manner across the whole range of peak METs. For both CVM and SCD, the risks decreased with increasing peak METs up to 9.9 METs, beyond which there were no further decreases in risks. However, for SCD, there was no significant benefit at peak METs > 13 METs. The relationship between peak METs and AF appeared U or reverse J shaped, and the upper threshold of risk reduction occurred at 9.9 METs, with no significant benefit at > 13 METs.

Discussion.

Our novel findings indicate that there is no upper limit of ACM benefit associated with increased levels of fitness. The upper threshold of CVM, SCD, and AF benefits occurred at 9.9 METs, suggesting that this fitness level confers multiple cardioprotective effects in middle-aged men aged 42 to 61 years. We observed that higher fitness, measured directly using the gold-standard method of expired gas analysis during cardiopulmonary exercise testing, was associated with decreased ACM in a linear dose-response manner with no evidence of a threshold effect; a finding which is in line with a previous report of no upper threshold for ACM benefit associated with increased levels of indirectly estimated fitness.[7] Therefore, it should be emphasized that higher fitness is largely associated with reduction in the risk of ACM

("higher is better"). The dose-response relation between PA level and CVM benefits is consistent with a curvilinear or a reverse J shape according to recent meta-analysis.[1,2] Our results appear similar to that of previous studies and we observed the risk reduction of CVM and SCD with increased fitness occurred at a peak of about 10 METs, largely consistent with an L shaped curve. However, there was neither additional risk reduction nor evidence of harm observed beyond this point. Though at fitness levels > 13 METs, there was still significant benefit for CVM, there was no benefit for SCD. Therefore, it should be emphasized that CVM and SCD benefits were attenuated at the highest level of fitness ("higher is not always better"). A meta-analysis and recent state-of-the-art review of AF indicated an inverse association between fitness and the risk of AF.[8,9] However, it is unclear whether higher fitness results in the greater benefit or little is known about the point of fitness where the benefits diminish or there is a decrease in the risk of AF. We observed a reverse J shaped relationship between fitness and AF, and the upper threshold of risk reduction benefit occurred at 9.9 METs, with no additional risk reduction observed beyond this point. These results are potentially consistent with previous studies, which demonstrate that extreme levels of PA increase the risk of AF.[10]

Conflict of Interests

The authors report no conflict of interests.

Keywords: Cardiorespiratory Fitness, dose response relation, mortality

Sae Young Jae (Department of Sport Science, University of Seoul, Seoul, South Korea)

Signature:

Sudhir Kurl (Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland)

Signature:

Hyun Jeong Kim (Department of Sport Science, University of Seoul, Seoul, South Korea)

Signature:

Barry A Franklin (Preventive Cardiology and Cardiac Rehabilitation, William Beaumont Hospital, Royal Oak, MI, USA)

Signature:

Setor K Kunutsor (Translational Health Sciences, Bristol Medical School, Southmead Hospital, University of Bristol, UK)

Signature:

Mira Kang (Center for Health Promotion, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea)

Signature:

Jari A Laukkanen (Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland)

Signature:

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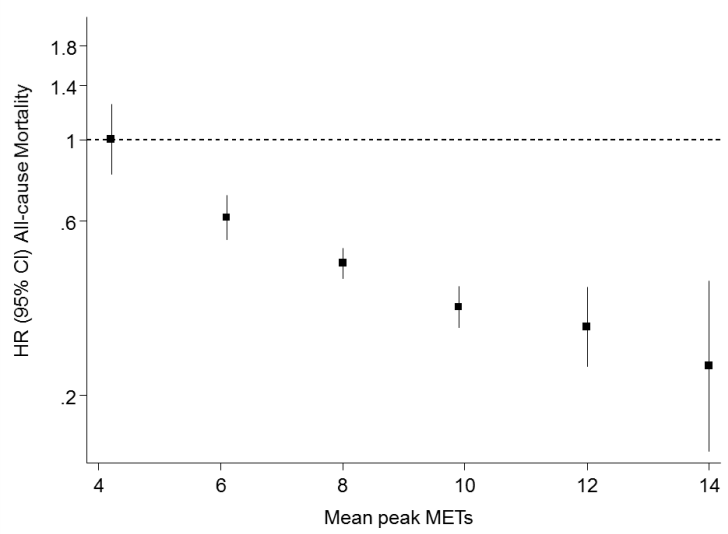
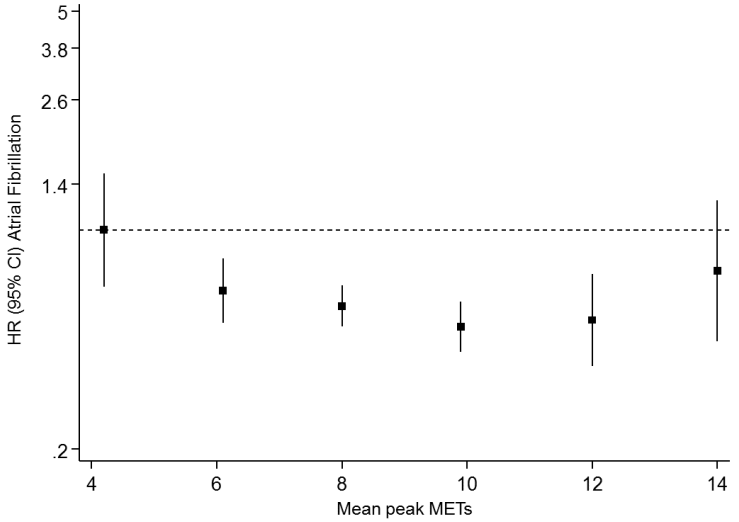
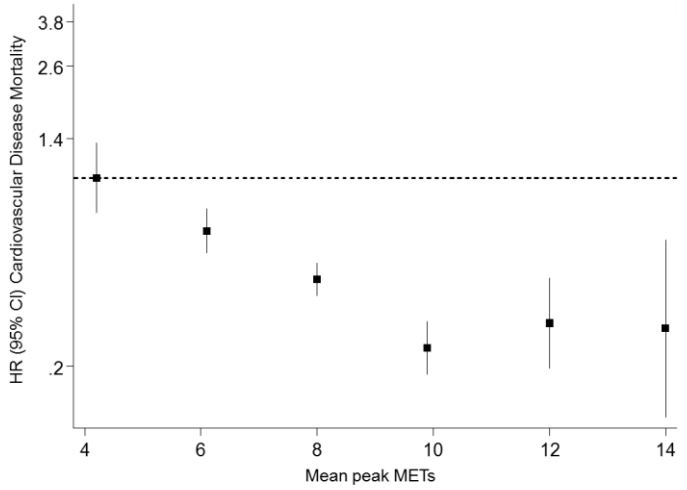
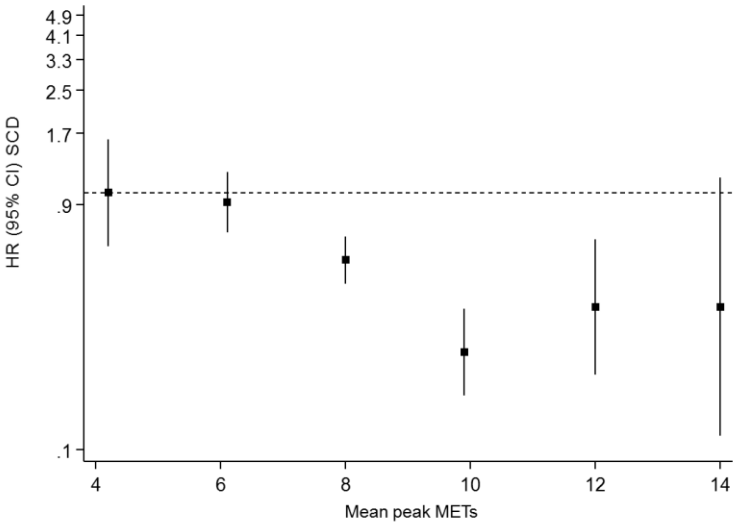
Figure 1. The hazard ratios of all-cause mortality, cardiovascular mortality, sudden cardiac death, and atrial fibrillation according to increased cardiorespiratory fitness levels after adjusted for age, body mass index, smoking, systolic blood pressure, total cholesterol, glucose,

C-reactive protein, and physical activity,


HR (95% CI) All-cause Mortality
1.8
1.4
1
.6
.2
4
6
8
10
12
14
Mean peak METs


HR (95% CI) Atrial Fibrillation
5
3.8
2.6
1.4
.2
4
6
8
10
12
14
Mean peak METs


HR (95% CI) Cardiovascular Disease Mortality
3.8
2.6
1.4
.2
4
6
8
10
12
14
Mean peak METs


HR (95% CI) SCD
4.9
4.1
3.3
2.5
1.7
.9
.1
4
6
8
10
12
14
Mean peak METs